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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,357	07/13/2006	Moshe Baru	27048U	1205

20529 7590 01/06/2009

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EXAMINER
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ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
01/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,357	BARU ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-42 and 44-57* is/are pending in the application.

4a) Of the above claim(s) *52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-42,44 and 46-51, and 54-57* is/are rejected.

7)☒ Claim(s) *45 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after Non-final rejection filed September 17, 2008 is acknowledged. Claim 43 has been cancelled and new claims 53-57 have been added. Claims 28-42 and 44-57 are pending in this application. Claim 52 remains withdrawn from further consideration as being drawn to nonelected species. Claims 28-42, 44-51 and 53-57 are examined on the merits in this office action.

Declaration under 37 CFR 1.132

1. Declaration under 37 CFR 1.132 filed on September 17, 2008 has been considered.

Withdrawn Rejection

2. Claims 28-29, 32-33 and 39-43 rejected under 35 U.S.C. 102(e) as being anticipated by Zalipsky et al (US Patent No. 6,586,002) is hereby withdrawn in view of Applicant's amendment to the claims.

Maintained Rejection

35 U.S.C. 112, 1st

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. (Revised necessitated by amendments) Claims 44, 46-50, 54-56 are rejected are under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hemophilia, does not reasonably provide enablement for any other diseases, disorder or conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to a pharmaceutical composition wherein the polypeptide is copaxone, and the composition may be used for the treatment of a disease selected from the group consisting of multiple sclerosis, diabetic neuropathy, senile dementia, Alzheimer's disease, Parkinson's Disease, facial nerve (Bell's) palsy, glaucoma, Huntington's chorea, amyotrophic lateral sclerosis, status epilepticus, non-arteritic optic

neuropathy and vitamin deficiency. The invention is further drawn to a method for treating a patient suffering from a disease that is known to be treatable with a protein or polypeptide known to effectively treat the disease, comprising administering to a patient in need thereof a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of the protein or polypeptide and colloidal particles.

(2) The state of the prior art:

The Merck manual indicates that there are plethora of disorders known, for example, Anorectal, foot and ankle, vascular, joint, mediatinal and pleural, arrhythmias and conduction, valvular, peripheral arterial to name just a few (see Merck manual, Disorders enclosed). Additionally, the Merck manual indicates that there are numerous numbers of diseases, for example, diverticular, bullous, tubulointerstital, prostate diseases, coronary artery diseases, viral skin diseases, inflammatory bowel disease, cystic kidney disease, Alzheimer's disease, Parkinson's disease, Wilson's disease to name just a few (see Merck manual, Diseases enclosed). For example, Alzheimer's disease according to the Merck manual is chronic, global, usually irreversible deterioration of cognition. The main types of Alzheimer's disease are: vascular dementia, Lewy body dementia, frontal-temporal dementias, and HIV-associated dementia (See Merck manual, "Dementia", Etiology and Classification, 2nd paragraph). Furthermore, Alzheimer's disease causes progressive cognitive deterioration and is characterized by senile plaques, beta-amyloid deposits, and neurofibrillary tangles in the cerebral cortex and subcortical gray matter (see Merck manual in Dementia under

"Alzheimer's disease). Furthermore, the Merck manual indicates that most cases are sporadic, with late onset and unclear etiology (see Merck manual, "Alzheimer's disease", Etiology and Pathophysiology). Since symptoms, signs are similar to those of other dementia, distinguishing Alzheimer's disease from other dementias is difficult (see Merck Manual, "Alzheimer's disease", Symptoms, Signs, and Diagnosis). Furthermore, Mattson MP (Nature, 2004, 430: 631-639) indicates that the risk of Alzheimer's disease (AD) dramatically increases in individuals beyond the age of 70 (see p. 631, left column, 1st sentence). The vast majority of cases of AD are sporadic, they do not run in families…molecular genetic analyses suggest that there are likely many genes that influence one's susceptibility to AD (see p. 633, left column, 2nd paragraph). Additionally, Mattson indicates that although drugs can temporarily improve memory, at present there are no treatments that can stop or reverse the inexorable neurodegenerative process (see abstract).

The Merck manual indicates that Multiple Sclerosis (MS) is characterized by disseminated patches of demyelination in the brain and spinal cord. Common symptoms include visual and oculmotor abnormalities, parensthesia, weakness, spasticity, urinary dysfunction, and mild cognitive impairment (see Merck manual, p. 1). The website www.copaxone.com indicates that COPAXONE® is useful for multiple sclerosis therapy (see p. 1 of www.copaxone.com). Steinman et al teach that "MS is a complicated disease, the cause and the pathogenesis of which are incompletely understood…Whether MS is actually a single disease or whether it is a primarily or initially an 'immune disease,' 'an infectious disease,' 'an inflammatory disease,' or a

'degenerative disease,' or a combination of all these types are all question with answers that are currently unknown" (see p. 12). Sriram et al state that the "[a]lthough the cause and pathogenesis of multiple sclerosis (MS) are unknown, current prevailing hypothesis favors MS to represent an autoimmune disorder directed against the nervous system antigen. The basic concept poses that exposure to environmental pathogens activates the autoreactive T cells that recognize the central nervous system (CNS) antoantigens, leasing to inflammation and demyelination. This belief is promoted by some similarities between MS and various animal models of experimental allergic encephalitis (EAE)" (see p. 939). Even though the art recognizes EAE as a model of MS, Sriram et al states that "EAE is a disorder that differs immunogenically and pathologically between species, according, in part, to the type of antigen used to induce it and the species in which the model is tested. None of the EAE models represents MS and they therefore are imprecise methods to elucidate either the pathogenesis or to develop therapeutic strategies in MS" (see p. 943).

In regards to "treating cancers" (A method for treating a patient suffering from a disease that is known to be treatable with a protein or polypeptide known to effectively treat the disease), Merck manual indicates that cancer is an unregulated proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and often, metastasis. Cancer can develop in any tissue or organ at any age. Furthermore, the Merck manual indicates that many cancers are curable if detected at an early stage, and long-term remission is often possible in later stages. However, cure is not always possible and is not attempted in some

advanced cases in which palliative care provides better quality of life than vigorous but fruitless attempts at tumor eradication (see Merck manual, Introduction). Additionally, the Merck manual indicates that malignancy may lead to pain, wasting, neuropathy, nausea, anorexia, seizures, hypercalcemia, hyperuricemia, or obstruction…Death typically occurs as a result of sudden or progressive failure of one or multiple organ systems (see Merck manual, Clinical Aspects of Cancer). Furthermore, a complete history and physical examination may reveal unexpected clues early cancer (see Merck manual, Clinical Aspects of Cancer, Diagnosis).

Furthermore, arts indicate the difficulties in going from *in vitro* to *in vivo* for drug development for treatment of cancers. Auerbach et al (Cancer and Metastasis Reviews, 2000, 19: 167-172) indicates that one of the major problems in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic response. For example, the 96 well rapid screening assay for cytokinesis was developed in order to permit screening of hybridoma supernatants…*In vitro* tests in general have been limited by the availability of suitable sources for endothelial cells, while *in vivo* assays have proven difficult to quantitate, limited in feasibility, and the test sites are not typical of the *in vivo* reality (see p. 167, left column, 1st paragraph). Gura T (Science, 1997, 278(5340): 1041-1042, encloses 1-5) indicates that "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all" (see p. 1, 2nd paragraph). Furthermore, Gura T indicates that the results of xenograft screening turned out to be not much better than those obtained with the original models, mainly because the xenograft rumors don't behave like naturally occurring tumors in

humans—they don't spread to other tissues, for example (see p. 2, 4th paragraph). Further, when patient's tumor cells in Petri dishes or culture flasks and monitor the cells' responses to various anticancer treatments, they don't work because the cells simply fail to divide in culture, and the results cannot tell a researcher how anticancer drugs will act in the body (see p. 3, 7th paragraph). Furthermore, Jain RK (Scientific American, July 1994,58-65) indicates that the existing pharmacopoeia has not markedly reduced the number of deaths caused by the most common solid tumors in adults, among them cancers of the lung, breast, colon, rectum, prostate and brain (see p. 58, left most column, 1st paragraph). Further, Jain RK indicates that to eradicate tumors, the therapeutic agents must then disperse throughout the growths in concentrations high enough to eliminate every deadly cells…solid cancers frequently impose formidable barriers to such dispersion (see p. 58, bottom of the left most column continuing onto the top of the middle column). Jain RK indicates that there are 3 critical tasks that drugs must do to attack malignant cells in a tumor: 1) it has to make its way into a microscopic blood vessel lying near malignant cells in the tumor, 2) exit from the vessel into the surrounding matrix, and 3) migrate through the matrix to the cells. Unfortunately, tumors often develop in ways that hinder each of these steps (see p. 58, bottom of right most column). Thus, the art recognizes that going from *in vitro* studies to *in vivo* studies for cancer drug developments are difficult to achieve.

The art recognizes that there are countless different conditions, disorders and diseases, but does not provide how to determine the individuals who are susceptible to any disorder, condition or disease list provided by the Merck manual.

With regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable.

Rudinger (Peptide Hormones, JA Parsons, Ed., 1976, 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study" (see p. 6). Additionally, SIGMA states that with regards to design of peptide sequences that, "Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine" (see p. 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility.

With regards to prediction of the native conformation of a protein (structure), the art is unpredictable. Berendsen (Science, 1998, 282: 642-643) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics" (see p. 642). Furthermore, Berendsen states that "Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field" (see p. 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). Voet et al teaches that the mutant hemoglobin HbE [GluB8(26)β to Lys] has, "no clinical manifestations in either heterozygotes or homozygotes" (see p. 235). Further, Hb Boston and Hb Milwaukee both have single point mutations which results in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state. Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state) (see p. 236). Further, HbS is a single point mutation, Val to GluA3(6)β (see p. 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. Therefore, making any polypeptide having any lengths amino acids that has the same activity as the claimed polypeptide, one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

The art provide guidance as to how to treat cancers and treating multiple sclerosis using COPOXANE®, but do not provide guidance as how to how to determine individuals who are susceptible to cancers, multiple sclerosis, and other critical illnesses (Alzheimer's disease, Huntington's, Parkinson's, ALS etc) and treating other diseases, such as diabetic neuropathy or glaucoma utilizing COPOXANE®.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on the determination of predicting those who are susceptible to cancers, multiple sclerosis, and other critical illnesses, for example. Since the activity is based on determining the patient population that is susceptible to cancers and other critical illnesses, the predictability in the art is low. This is due to the fact that the art has recognized the difficulty in determining the patient population who are susceptible to these diseases. This is due to the fact that the art has recognized that there are plethora of different conditions, disorders and diseases, but does not provide how to determine the individuals who are susceptible to any disorder, condition or disease list provided by the Merck manual. For example, not all elderly people over 65 years of age suffer from Alzheimer's disease. Additionally, not everyone suffers from prostate cancer or AIDS.

As described above, Alzheimer's disease causes progressive cognitive deterioration and is characterized by senile plaques, beta-amyloid deposits, and neurofibrillary tangles in the cerebral cortex and subcortical gray matter (see Merck manual in Dementia under "Alzheimer's disease). Furthermore, the Merck manual indicates that most cases are sporadic, with late onset and unclear etiology (see Merck manual, "Alzheimer's disease", Etiology and Pathophysiology). Since symptoms, signs are similar to those of other dementia, distinguishing Alzheimer's disease from other dementias is difficult (see Merck Manual, "Alzheimer's disease", Symptoms, Signs, and Diagnosis). Furthermore, Mattson MP (Nature, 2004, 430: 631-639) indicates that the risk of Alzheimer's disease (AD) dramatically increases in individuals beyond the age of 70 (see p. 631, left column, 1st sentence). The vast majority of cases of AD are sporadic, they do not run in families…molecular genetic analyses suggest that there are likely many genes that influence one's susceptibility to AD (see p. 633, left column, 2nd paragraph). Additionally, Mattson indicates that although drugs can temporarily improve memory, at present there are no treatments that can stop or reverse the inexorable neurodegenerative process (see abstract).

Further, "MS is a complicated disease, the cause and the pathogenesis of which are incompletely understood…Whether MS is actually a single disease or whether it is a primarily or initially an 'immune disease,' 'an infectious disease,' 'an inflammatory disease,' or a 'degenerative disease,' or a combination of all these types are all question with answers that are currently unknown."

The claims don't identify the type of disorder, condition or disease, therefore, the claim implies that anyone can be treated from any disorder, condition or disease. However, the Applicant has not shown who will be susceptible to disorder, condition or disease and the types of disorder, condition or disease. There are too many variables between the patient populations, thus, it clearly shows the unpredictability of the art.

With regards to the effect of amino acid substitution in a peptide or protein, given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. Therefore, making any peptide having at least 18 amino acids that has the same activity as the claimed peptide, one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

(5) The breadth of the claims:

The claims are drawn to a pharmaceutical composition wherein the polypeptide is COPAXONE®, and the composition may be used for the treatment of a disease selected from the group consisting of multiple sclerosis, diabetic neuropathy, senile dementia, Alzheimer's disease, Parkinson's Disease, facial nerve (Bell's) palsy, glaucoma, Huntington's chorea, amyotrophic lateral sclerosis, status epilepticus, non-

arteritic optic neuropathy and vitamin deficiency. The invention is further drawn to a method for treating a patient suffering from a disease that is known to be treatable with a protein or polypeptide known to effectively treat the disease, comprising administering to a patient in need thereof a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of the protein or polypeptide and colloidal particles. from method of treatment of a patient suffering from a disease comprising administrating to the patient a pharmaceutical composition of protein or polypeptide and colloidal particles.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

Although the specification provides guidance on how to make the composition and administer the compound, it is unclear as to when to administer the compound and the patient population. The specification discloses that hemophilia A are prone to frequent hemorrhages as a result of one or more misfunctions of the coagulation system (see p. 1, lines 6-7). The specification discloses that one of the causes of hemophilia is a shortage of Factor VIII in the blood and this problem can be treated with Factor VIII concentrates; however, in about 15% of the patients that occurrence results of Factor VIII neutralizing antibodies, so-called inhibitors, whereby a therapy with Factor VIII concentrates is hardly possible (see p. 1, lines 7-11). The specification discloses SCC injection of liposome-formulated G-CSF into mice, and pharmacokinetic parameters were calculated for each mouse (see p. 15, lines 8-13). Furthermore, the specification

discloses the pharmacokinetic parameters following IV injection of Factor IX or PEGylated liposome-formulated Factor IX into mice (see p. 15, line 15). The specification further discloses the biological activity of factor VIII that was formulated in-vivo with PEGylated liposomes by injection of liposomes 1 hour after the injection of unformulated factor VIII in hemophiliac mice. The specification discloses that the results indicate that the half-life and are under the curve of factor VIII that was formulated in vivo with PEGylated liposomes were higher than that of free FVIII (see Example 11). Additionally, the specification discloses that factor VIIa is generally used to treat hemophilia patients with inhibitors and to stop trauma bleeding. FVIIa formulated with PEGylated liposomes were injected into mice, and the rats were bled at various times post-injection and FVIIa activity was measured by a clotting assay and the results indicate that the half-life and are under the curve of FVIIa that was formulated in-vivo with PEGylated liposomes were higher than that of free FVIIa (see Example 13). There are not enough working examples for guidance. For example, as explained above, the specification only describes treatment of hemophilia, utilizing factor VIII, IX and VIIa.

The specification has not provided guidance in the way of a disclosure to how to determine individuals that need protection against any disorder, condition or disease. The specification discloses that the invention is particularly suited to patients previously diagnosed with prostate cancer. The specification discloses that the non-natural amino acid polypeptides, modified or unmodified, can be administered directly to mammalian subject by any of the routes normally used for introducing a polypeptide to a subject (see paragraph [0955]). Furthermore, the specification discloses that the effective

amount of the formulation to be administered in the treatment or prophylaxis of disease (including but not limited to cancers, inherited diseases, diabetes, AIDS, or the like) (see paragraph [0951]). The specification does not disclose how to treat diabetic neuropathy, senile dementia, Alzheimer's disease, Parkinson's disease, Huntington's chorea, ALS and other diseases by administering COPAXONE® to a patient.

Although working examples are not required by the MPEP, but the lack of working examples are factors to be considered under an enablement analysis. This is especially true when the method or treatment proposed is unpredictable. As stated above, Steinman et al teach that "MS is a complicated disease, the cause and the pathogenesis of which are incompletely understood…Whether MS is actually a single disease or whether it is a primarily or initially an 'immune disease,' 'an infectious disease,' 'an inflammatory disease,' or a 'degenerative disease,' or a combination of all these types are all question with answers that are currently unknown."

As described supra, the Merck manual indicates that cancer is an unregulated proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and often, metastasis. Cancer can develop in any tissue or organ at any age. Furthermore, the Merck manual indicates that many cancers are curable if detected at an early stage, and long-term remission is often possible in later stages. However, cure is not always possible and is not attempted in some advanced cases in which palliative care provides better quality of life than vigorous but fruitless attempts at tumor eradication (see Merck manual, Introduction). Additionally, the Merck manual indicates that malignancy may lead to pain, wasting,

neuropathy, nausea, anorexia, seizures, hypocalcaemia, hyperuricemia, or obstruction…Death typically occurs as a result of sudden or progressive failure of one or multiple organ systems (see Merck manual, Clinical Aspects of Cancer). Furthermore, a complete history and physical examination may reveal unexpected clues early cancer (see Merck manual, Clinical Aspects of Cancer, Diagnosis). Furthermore, arts indicate the difficulties in going from *in vitro* to *in vivo* for drug development for treatment of cancers. Auerbach et al (Cancer and Metastasis Reviews, 2000, 19: 167-172) indicates that one of the major problems in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic response. For example, the 96 well rapid screening assay for cytokinesis was developed in order to permit screening of hybridoma supernatants…*In vitro* tests in general have been limited by the availability of suitable sources for endothelial cells, while *in vivo* assays have proven difficult to quantitate, limited in feasibility, and the test sites are not typical of the *in vivo* reality (see p. 167, left column, 1st paragraph). Gura T (Science, 1997, 278(5340): 1041-1042, encloses 1-5) indicates that "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all" (see p. 1, 2nd paragraph). Furthermore, Gura T indicates that the results of xenograft screening turned out to be not much better than those obtained with the original models, mainly because the xenograft rumors don't behave like naturally occurring tumors in humans—they don't spread to other tissues, for example (see p. 2, 4th paragraph). Further, when patient's tumor cells in Petri dishes or culture flasks and monitor the cells' responses to various anticancer treatments, they don't work because the cells simply

fail to divide in culture, and the results cannot tell a researcher how anticancer drugs will act in the body (see p. 3, 7th paragraph). Furthermore, Jain RK (Scientific American, July 1994,58-65) indicates that the existing pharmacopoeia has not markedly reduced the number of deaths caused by the most common solid tumors in adults, among them cancers of the lung, breast, colon, rectum, prostate and brain (see p. 58, left most column, 1st paragraph). Further, Jain RK indicates that to eradicate tumors, the therapeutic agents must then disperse throughout the growths in concentrations high enough to eliminate every deadly cells…solid cancers frequently impose formidable barriers to such dispersion (see p. 58, bottom of the left most column continuing onto the top of the middle column). Jain RK indicates that there are 3 critical tasks that drugs must do to attack malignant cells in a tumor: 1) it has to make its way into a microscopic blood vessel lying near malignant cells in the tumor, 2) exit from the vessel into the surrounding matrix, and 3) migrate through the matrix to the cells. Unfortunately, tumors often develop in ways that hinder each of these steps (see p. 58, bottom of right most column). Thus, the art recognizes that going from *in vitro* studies to *in vivo* studies for cancer drug developments are difficult to achieve.

With regards to prediction of the native conformation of a protein (structure), the art is unpredictable. Berendsen (Science, 1998, 282: 642-643) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics" (see p. 642). Furthermore, Berendsen states that "Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do

not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field" (see p. 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). Voet et al teaches that the mutant hemoglobin HbE [GluB8(26)β to Lys] has, "no clinical manifestations in either heterozygotes or homozygotes" (see p. 235). Further, Hb Boston and Hb Milwaukee both have single point mutations which results in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state. Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state) (see p. 236). Further, HbS is a single point mutation, Val to GluA3(6)β (see p. 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. Therefore, making any polypeptide having any lengths

amino acids that has the same activity as the claimed polypeptide (where R1 and R2 are polypeptides), one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

There is no clear guidance as to how to determine the patient population, since not all people suffer from the same disorder, condition or disease. Since art recognizes that there are countless different conditions, disorders and diseases, but does not provide how to determine the individuals who are susceptible to any disorder, condition or disease list provided by the Merck manual, more guidance is necessary.

(8) The quantity of experimentation necessary:

In order to treat a disease, a dosage, the subject and regimen must be identified. In order to ameliorate a disease symptoms or conditions, the end point of the treatment also needs to be identified. Since it is uncertain to predict the patient population who are susceptible for unknown disorder, condition or disease, and the Applicant have not provided the appropriate time frame at which the compound should be administered, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the compound would be effective in treating an adult, child, or an infant from all disorder, condition or disease (such as treating cancers, multiple sclerosis and other critical illnesses, (Alzheimer's disease, Huntington's disease, ALS, glaucoma, etc). Considering the state of the art as discussed by the reference above and the high unpredictability and the lack of guidance

provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to make polypeptide comprising S/T-X-L/I/V-I/V/Q/S-S/T-X-X-E that would treat all diseases and test whether COPAXONE® has a therapeutic activity that treats would treat diseases selected from Alzheimer's disease, Parkinson's disease, facial nerve (Bell's) palsy, glaucoma, Huntington's chorea, ALS, status epilepticus, non-arteritic optic neuropathy and vitamin deficiency.

Response to Applicant's Arguments

5. Applicant argues that "the specification, figures, and experimental examples, provide ample guidance to the skilled artisan in view of the state of the art at the time the application was filed, to make and use the claimed subject matter without undue experimentation. Moreover, Applicants submit that diseases known to be treatable with a protein or polypeptide known to effectively treat the disease the disease known to be treatable with a protein or polypeptide known to effectively treat the disease...proteins or polypeptides that comprise a consensus sequence of S/T-X-L/I/V-I/V/Q/S-S/T-X-X-E, where X may be any amino acid, and S, T, L, I, V, E and Q have their standard meanings, are within the knowledge of one of ordinary skill in the art to which the present subject matter applies." Applicant further argues that "Applicants provide herewith a copy of a second Declaration under 37 CFR 1.132, executed by Dr. Moshe Baru, along with Annex A which describes experimental results that are discussed in the second Declaration. As indicated by Dr. Baru…the treatment of colitis differs significantly from the treatment of hemophilia." Applicant argues that "the Declaration

and attached Annex A provide evidence that the claims are sufficiently enabled for a scientist skilled in the relevant art to apply the claimed subject matter to other proteins and polypeptide." Applicant further argues that "The present specification describes and exemplifies, suitable coupling reactions as well as the binding of proteins/polypeptides to liposomes…the present specification does describe and provide examples where the therapeutic polypeptides are modified or conjugated to the surface of PEG or liposomes." Applicant further argues that "Copoxane is known for treatment of inflammatory bowel disease (IBD) (2nd Declaration)."

6. Applicant's arguments have been fully considered but have not been found persuasive. The claims are broadly drawn to a method of treatment of a patient suffering from a disease that is treatable by any protein and polypeptide having the consensus sequence S/T-X-L/I/V-I/V/Q/S-S/T-X-X-E. Furthermore, the amended claim 44 is drawn to the pharmaceutical composition of claim 28 wherein the polypeptide is Copaxone, and the composition may be used for the treatment of a disease selected from multiple sclerosis, diabetic neuropathy, senile dementia, Alzheimer's disease, Parkinson's Disease, facial nerve (Bell's) palsy, glaucoma, Huntington's chorea, amyotrophic lateral sclerosis, status epilepticus, non-arteritic optic neuropathy and vitamin deficiency. The treatment of disease, disorder or condition has no bearing on the compound or the composition. Furthermore, the art recognizes that there are plethora of disorders known, for example, Anorectal, foot and ankle, vascular, joint, mediatinal and pleural, arrhythmias and conduction, valvular, peripheral arterial to name just a few. The disorders, condition or diseases involve different cells, different organs

of the body and different mechanisms. The therapeutic polypeptide that is utilized to treat one type of cancer may not treat other types of cancer. For example, a therapeutic polypeptide that treats prostate cancer or tumor may not treat other types of cancer such as lung, breast or leukemia. There is plethora of types of cancer. However, not one single therapeutic polypeptide treats all types of cancer. Furthermore, a person suffering from diabetes will have other diseases associated with the disease, such as heart condition, obesity, and high blood pressure. A therapeutic polypeptide, such as insulin, GLP-1, etc that are known for treating diabetes would not necessarily treat heart conditions, obesity or high blood pressure. Therefore, a therapeutic polypeptide to treat one disorder, condition or disease would not treat other disorder, condition or diseases. Claims 47 and 50-51 are drawn to a method of treatment of a patient suffering from a disease comprising administrating a pharmaceutical composition of a protein or polypeptide and colloidal particle. In regards to Tompkins reference, there is a nexus between G-CSF and treating Multiple Sclerosis. However, Tompkins reference and the specification does not disclose treating ALL diseases using G-CSF or any other colloidal conjugated peptide/protein. Granulocyte colony-stimulating factor is a growth factor that stimulates the bone marrow to make more white blood cells. In regards to the 132 Declaration (2^{nd}), the data is only directed to the IBD and Copaxone. The Applicant has not shown that Copaxone is useful in treating other diseases, such as Alzheimer's disease, Parkinson's disease, glaucoma, Huntington's disease, ALS, or vitamin deficiency, for example.

Furthermore, the therapeutic polypeptides are different amino acids in lengths: G-CSF (GenBank P35834) has 175 amino acid residues; GLP-1 (GenBank Accession No. NP_002045) has 185 amino acid residues; prothrombin (GenBank AAB24476) has 64 amino acid residues. Furthermore, the specification does not provide any examples as where these therapeutic polypeptides are modified or conjugated to the surface of PEG or liposome. The peptides listed above, G-CSF, GLP-1 and prothrombin each have multiple glutamic acid residues that may form bonds to the PEG or liposome; additionally, these peptides have multiple arginine and lysine residues that can form bonds to PEG or liposome. In regards to Applicant's arguments that "the specification describes suitable coupling reactions as well as the binding of proteins/polypeptides to liposomes", as described above, there are multiple glutamic acid, lysine and arginine residues that can form bonds to PEG or liposome, and therefore, the specification has not described how the therapeutic polypeptides are modified or conjugated to the surface of PEG or liposomes. Applicant indicates that "in Examples 9-10, at page 13, lines 13-20, describes the following with regard to a formulation of FIX and G-CSF with PEGylated liposomes…by dissolving the protein with liposome solution." However, this still does not disclose how and where the polypeptides are modified or conjugated to the surface of the PEG or liposomes.

Therefore, there are multiple sites where the therapeutic polypeptides can be conjugate to the PEG or liposomes. Furthermore, modification of therapeutic polypeptide incorporating the PEG or liposomes is not known to maintain the therapeutic effectiveness for ALL polypeptides. Thus, vast numbers of experimentation

would be required to see if the polypeptide conjugated to PEG or liposome would have the same affect on certain diseases as the wild-type polypeptides. Additionally, the instant specification discloses that Interferon-γ comprises the consensus sequence S/T-X-L/I/V-I/V/Q/S-S/T-X-X-E. However, the sequence SQIVS (see FIG. 8A) does not comprise ALL of the consensus sequence as claimed. Furthermore, prediction of the native conformation of a protein (structure), the art is unpredictable. Berendsen (Science, 1998, 282: 642-643) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics" (see p. 642). Furthermore, Berendsen states that "Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field" (see p. 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). Voet et al teaches that the mutant hemoglobin HbE [GluB8(26)β to Lys] has, "no clinical manifestations in either heterozygotes or homozygotes" (see p. 235). Further, Hb Boston and Hb Milwaukee both have single point mutations which results in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state.

Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state) (see p. 236). Further, HbS is a single point mutation, Val to GluA3(6)β (see p. 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. Therefore, making any polypeptide having any lengths amino acids that has the same activity as the claimed polypeptide (where R1 and R2 are polypeptides), one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

Furthermore, the specification does not disclose treatment of diabetic neuropathy, senile dementia, Alzheimer's disease, Parkinson's Disease, facial nerve (Bell's) palsy, glaucoma, Huntington's chorea, ALA, status epilepticus, non-arteritic optic neuropathy, and vitamin deficiency utilizing COPAXONE®. The 1.132 Declaration filed on September 17, 2008 indicate the treatment of IBD utilizing COPAXONE®.

Again, the claimed invention is enabling for treating hemophilia, but the specification does not reasonably provide enablement for any other diseases, disorder or conditions, such as Alzheimer's disease, ALS, glaucoma, and vitamin deficiency.

35 U.S.C. 112, 1st

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 28-42, 46-51, 54-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level

of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of

representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, the colloidal particle comprising 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer. The generic statements protein or polypeptide, protein or polypeptides that include a consensus sequence of S/T-X-L/I/V-I/V/Q/S-S/T-XX-E, where X may be any amino acid do not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claims 28 and 55 are broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule that can form peptide bonds, and make up the class of proteins or polypeptides. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is “not sufficient characteristic for written description purposes, even when accompanied by a method of

obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives, variants or homologs. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule or other peptidic molecules that can form peptide bonds, other synthetic peptide or peptide-like molecule, peptidomimetics or amino acid mimetics that can function as proteins or polypeptides that can bind to polymer or colloidal particles.

The specification is limited to the peptide or peptide-like molecules that belong to coagulation factors (Factor X, Factor VIIa, Factor IX, Factor X), granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), interferon-γ, and Glucagon like peptide-1 (GLP-1). The working examples 1-8 describe the liposome preparation, and binding the proteins/polypeptides to PEGlyated Liposomes. The examples disclose that the DSPE-PEG2000 binding to FVIII, and the binding analysis was by Surface Plasmon Resonance measurement (comparing control liposomes with protein/peptide bound PEG-liposomes (see paragraphs [0043]-[0044]). Same experiments were performed on other recombinant and purified proteins: G-CSF, GM-CSF, Interferon and GLP-1 (see paragraph [0046]). Examples 9-10 disclose pharmacokinetics of liposome-formulated G-CSF and free G-CSF in mice. Example 11

describes the pharmacokinetics and biological activity of FVIII formulated PEGylated Liposomes in hemophilic mice in vivo (see paragraphs [0063]-[0064]). The specification does not describe any protein and polypeptide, or any other type of peptide or peptide-like molecule that functions a protein and polypeptide. Furthermore, the specification does not describe how the PEG-liposome is conjugated to the protein/polypeptide. Description of FVII, FIX, G-CSF, GM-CSF, IFN-γ, EPO, Human growth factor, Interferon-α2a, Interfereon-α2b, GLP-1 is not sufficient to encompass numerous other proteins and polypeptide that belong to the same genus. Furthermore, a protein or polypeptide having a consensus sequence S/T-X-L/I/V-I/V/Q/S-S/T-XX-E, where X may be any amino acid lead to many different peptide consensus sequences. For example, there are 20 naturally occurring amino acids, therefore X can be any 20 of the naturally occurring amino acids. Furthermore, there are three X's in the sequence. This lead to further variations to the consensus sequence. There are non-naturally occurring amino acids, such as D-amino acids, b-amino acids, g-amino acid and e-amino acids. When these are factored into the equation, there are even greater numbers of possibilities for the consensus sequence. Additionally, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will

hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Applicant's Arguments

9. Applicant argues that "the specification complies with the written description requirement for presently pending claims 28-42 and 46...Specifically, claim 28 now recites the following proteins or polypeptides; Factor VIIa, G-CSF, GM-CSF, interferon γ, GLP-1 and Copaxone." Further Applicant argues that "a simple calculation shows that the consensus sequence substantially limits the number of possible combination by 67, 368 times...Thus, the consensus sequence is limited to 0.000015 of all possible sequences."

10. Applicant's arguments have been fully considered but have not been found persuasive. The claims 28 and 55 are drawn to "a protein or polypeptide selected from the group consisting of Factor VIIa, G-CSF, GM-CSF, interferon γ, GLP-1 and Copaxone; or proteins or polypeptides that comprise a consensus sequence of S/T-X-L/I/V-I/V/Q/S-S/T-X-X-E. The specification does not describe how the PEG-liposome is conjugated to the protein/polypeptide. Description of FVII, FIX, G-CSF, GM-CSF, IFN-γ, EPO, Human growth factor, Interferon-α2a, Interfereon-α2b, GLP-1 does not provide ample examples of all of possible proteins or polypeptides having the consensus sequence. As Applicant indicates, there are $25.6 \times 10^9 / 3.8 \times 10^5 = 67{,}368$ different

possibilities. Applicant has not provided enough examples and provided enough proteins or polypeptides that encompass the proteins and polypeptides comprising the consensus sequence S/T-X-L/I/V-I/V/Q/S-S/T-X-X-E. Therefore, Applicant was not in possession of all of the proteins and polypeptides at the time of filing of the instant application.

35 U.S.C. 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 28-32, 36-37, 39-42, 46 and 55-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Baru M (WO 99/55306, filed in the IDS 2/15/2006).

13. Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles. The particles comprise approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer which carries substantially no net charge. The protein or polypeptide is capable of externally binding the colloidal particles, or is capable of binding polyethylene glycol and is not encapsulated in the colloidal particle (see abstract). Furthermore, the reference teaches that the term “proteins or polypeptides capable of externally binding said colloidal particles” includes proteins and polypeptides which, similarly to FVIII, binds to

membranes comprising phosphatidylcholine:phosphatidylserine (PC:PS); non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V (see p.7, lines 6-12, claims 18-19), which meets the limitations of claims 28-29, 32 and 36-37. The reference further teaches that the colloidal particle has a mean particle diameter of between about 0.05 to about 0.4 microns, and approximately 0.1 microns (see claims 2-3), which meets the limitation of claims 30-31. It is noted that claim 30 has been rejected over the prior art, even though the reference does not disclose exact colloidal particle diameter range as claimed. However, both the claims and the reference utilize the term "about" when discussing the colloidal particle diameter. The term "about" allows for some tolerance in the ranges disclosed. In *In re Ayers*, the Federal Circuit held that "at least about 10%" was anticipated by a reference that disclosed "about 8%" because the term "about" allowed for some tolerance. *In re Ayers*, 154 F.2d 182, 185 (Fed. Cir. 1946). Similarly, in Johnson and Johnson v. W.L. Gore & Associates, Inc., the Court allowed for "about 1.2" to be inclusive of 1.0. See Johnson and Johnson v. W.L. Gore & Associates, Inc., 436 F.Supp. 704, 728-729 (Fed. Cir. 1977). Although about has never been confined to specific percentage of variability, the Johnson and Johnson decision at least implies that 16% variability is permissible when "about" is used (1.0/1.2 = ~16.6% variability). Thus, the term "about" implicitly discloses some variability even though the specification may not literally cite this variability. Thus, the disclosure of a colloidal particle diameter of "about" 0.05 μm encompasses a diameter of "about" 0.03 μm, as claimed. The reference further teaches that the amphipathic lipid is a phospholipid from natural or synthetic sources (see claim

4), which meets the limitation of claim 32. The reference further teaches that the biocompatible hydrophilic polymer is selected from group consisting of polyalkylether, polylactic and polyglycolic acid families, and is a polyethylene glycol (see claims 6-7), which meets the limitations of claims 39-40.The reference further teaches that the polyethylene glycol has a molecular weight of between about 1000 to about 5000 daltons (approximately 2000 daltons) (see claims 8-9), which meets the limitations of claims 41-42. The reference further teaches that "phospholipids used are synthetic and no-toxic, and can therefore, be used in vivo for therapeutic treatment…liposomes do not encapsulate FVIII, so that smaller sized liposomes can be sued which have a longer half-life in vivo, since they are not removed by the reticuloendothelial system (RES) (see p. 4, lines 1-6). Since non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V, this meets the limitation of claims 55-56.

Response to Applicant's Arguments

14. Applicant argues that "in contrast, Baru et al is directed to a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles…Baru et al describes that a preferred protein is factor VIII, whose half-life is extended and which is protected from serum inhibitor antibodies by injecting it as a component of the composition...amended claim 28 now recites the specific proteins or polypeptides in paragraphs (a) and (b). Baru et al does not describe any of the specific proteins or polypeptides recited in paragraphs (a) and (b) of amended claim 28."

15. Applicant's arguments have been fully considered, but have not been found persuasive. Baru reference teaches all of the components of the instant claims 28-32, 36-37 and 39-42. Baru teaches that non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V (see p. 7, lines 6-12, and claims 18-19). As evidenced by instant specification, "the term proteins or polypeptides capable of externally binding said colloidal particles includes proteins such as coagulation factor VIIa (FVIIa), factor V(FV), factor IX (FIX) and factor X (FX), Granulocyte colony-stimulating factor (G-CSF), Granulocyte macrophage colony-stimulating factor (GM-CSF), Interferon-γ, and GLP-1 (see paragraph [0016]). These peptides must have the consensus sequence of S/T-X-L/I/V-I/V/Q/S-S/T-XX-E, since FIG. 8A of instant specification discloses that FVIII, FIX, G-CSF, GM-CSF and GLP-1 comprise the consensus sequence. Baru reference teaches that the protein or polypeptide is non-covalently bound to one or more colloidal particles (see p. 7, lines 13-17). Therefore, the Baru reference anticipates the instant claims 28-32, 36-37 and 39-42.

New Rejection

35 U.S.C. 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 28-32, 36-37, 39-42, 46 and 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006).

20. Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles. The particles comprise approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer which carries substantially no net charge. The protein or polypeptide is capable of externally binding the colloidal particles, or is capable of binding polyethylene glycol and

is not encapsulated in the colloidal particle (see abstract). Furthermore, the reference teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, binds to membranes comprising phosphatidylcholine:phosphatidylserine (PC:PS); non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V (see p.7, lines 6-12, claims 18-19), which meets the limitations of claims 28-29, 32 and 36-37. The reference further teaches that the colloidal particle has a mean particle diameter of between about 0.05 to about 0.4 microns, and approximately 0.1 microns (see claims 2-3), which meets the limitation of claims 30-31. It is noted that claim 30 has been rejected over the prior art, even though the reference does not disclose exact colloidal particle diameter range as claimed. However, both the claims and the reference utilize the term "about" when discussing the colloidal particle diameter. The term "about" allows for some tolerance in the ranges disclosed. In *In re Ayers*, the Federal Circuit held that "at least about 10%" was anticipated by a reference that disclosed "about 8%" because the term "about" allowed for some tolerance. *In re Ayers*, 154 F.2d 182, 185 (Fed. Cir. 1946). Similarly, in Johnson and Johnson v. W.L. Gore & Associates, Inc., the Court allowed for "about 1.2" to be inclusive of 1.0. See Johnson and Johnson v. W.L. Gore & Associates, Inc., 436 F.Supp. 704, 728-729 (Fed. Cir. 1977). Although about has never been confined to specific percentage of variability, the Johnson and Johnson decision at least implies that 16% variability is permissible when "about" is used (1.0/1.2 = ~16.6% variability). Thus, the term "about" implicitly discloses some variability even though the specification may not literally cite

this variability. Thus, the disclosure of a colloidal particle diameter of "about" 0.05 μm encompasses a diameter of "about" 0.03 μm, as claimed. The reference further teaches that the amphipathic lipid is a phospholipid from natural or synthetic sources (see claim 4), which meets the limitation of claim 32. The reference further teaches that the biocompatible hydrophilic polymer is selected from group consisting of polyalkylether, polylactic and polyglycolic acid families, and is a polyethylene glycol (see claims 6-7), which meets the limitations of claims 39-40.The reference further teaches that the polyethylene glycol has a molecular weight of between about 1000 to about 5000 daltons (approximately 2000 daltons) (see claims 8-9), which meets the limitations of claims 41-42. The reference further teaches that "phospholipids used are synthetic and no-toxic, and can therefore, be used in vivo for therapeutic treatment…liposomes do not encapsulate FVIII, so that smaller sized liposomes can be used which have a longer half-life *in vivo*, since they are not removed by the reticuloendothelial system (RES) (see p. 4, lines 1-6). Since non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V, this meets the limitation of claims 55-56. The difference between the reference and the instant claims is that the reference does not teach the protein or polypeptide is selected from the group consisting of Factor VIIa, G-CSF, GM-CSF, interferon-γ, GLP-1 and Copaxone.

21. However, it would have been obvious to one of ordinary skill in the art to try other proteins and polypeptides. One of ordinary skill in the art would have been motivated to try other proteins and polypeptides, since Baru reference teaches that the Factor VIII, prothrombin, Factor V and Factor X would be successful, and phospholipids used do

not encapsulate FVIII, so that smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation of success, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide which are similar to FVIII, and include prothrombin, Factor X and Factor V.

Conclusion

22. Claims 45 and 53 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. No claim is allowed.

23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. H./
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654